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Full Papers

Enantioselective Ketone Hydrogenation: From R&D to Pilot Scale with Industrially Viable Ru/Phosphine−Oxazoline Complexes

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Abstract:

The development of a pilot process for the enantioselective hydrogenation of 3,5-bistrifluoromethyl acetophenone (BTMA) using a Ru/phosphine−oxazoline complex in toluene in the presence of aqueous NaOH is described. Various reaction parameters and quality risk factors such as ligand structure, substrate quality, reaction conditions, thermal safety, etc. were investigated. The reaction was carried out twice on a 140-kg scale at 20 bar and 25 °C with substrate-to-catalyst ratios of 20,000 with an enantiomeric excess of >95%. After crystallization, (*R*)-3,5-bistrifluoromethyl phenyl ethanol (BTMP) was obtained with an ee between 97.7 and 98.6% in 70% chemical yield.

Introduction

The enantioselective reduction of aryl ketones is an important transformation both from an academic/synthetic as well as an industrial point of view.[1] In addition to biocatalytic and hydride reduction methods, two different effective hydrogenation methodologies have been developed: (i) transfer hydrogenations, where the reducing agent is a hydrogen donor such as formic acid or isopropanol,[2] and (ii) the catalytic addition of gaseous H_2 to the ArC=O double bond.[3] From an industrial point of view both technologies have their advantages and disadvantages. While transfer hydrogenation reactions do not require the handling of hydrogen under relatively high pressure (using expensive equipment), hydrogenation catalysts are in most cases much more active and need significantly lower amounts of (rather expensive) catalysts. Interestingly, with few exceptions the two methods require different types of catalysts.[4] The choice

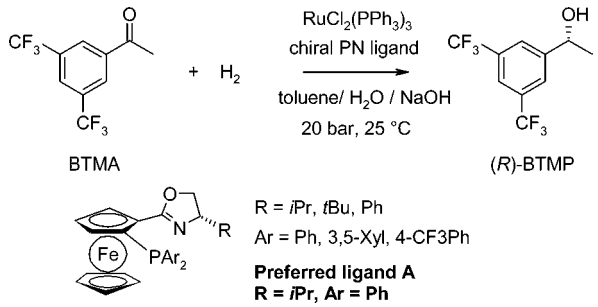

Figure 1. **Reaction conditions and structure of the phosphine−oxazoline ligands.**

to apply a specific technology is usually determined by the answer to the following three questions:

(1) Can the costs for the overall manufacturing process compete with alternative routes?

(2) Can the catalytic step be developed in the given time and cost frame with the equipment available?

(3) Is the method not patent protected, and/or are the licensing conditions appropriate?

Results and Discussion

We have recently developed novel and effective hydrogenation catalysts prepared in situ from $RuCl_2(PPh_3)_3$ and chiral phosphine−oxazoline ligands which are effective for the hydrogenation of various aryl ketones with ee's up to 99%.[5] Substrate/catalyst ratios of 10,000−50,000 can be reached, and—in contrast to most transfer hydrogenation systems—the reaction tolerates high substrate concentrations. Furthermore, a technically more practical toluene/aqueous NaOH mixture can be used instead of the usual *i*-PrOH/*i*-PrOK solution.

(*R*)-3,5-Bistrifluoromethyl phenyl ethanol (BTMP) is an interesting chiral building block for a number of pharmaceutically interesting targets such as an NK-1 receptor antagonist.[6] The most attractive route to BTMP is the enantioselective hydrogenation of 3,5-bistrifluoromethyl acetophenone (BTMA) as depicted in Figure 1. Since many

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Table 1. **Effect of ligand structure (see Figure 1) and reaction conditions[a] on ee and reaction time**

entry	ligand R/Ar	s/c	time (h)	conv. (%)	ee (%)	comments
1.1	*i*-Pr/Ph	500	19	100	94	ligand **A**, 50 °C
1.2	*t*-Bu/Ph	500	19	100	92	
1.3	Ph/Ph	500	19	100	93	
1.4	*i*-Pr/Xyl	500	19	100	92	Xyl = 3,5-Me_2Ph, 50 °C
1.5	*i*-Pr/Ar′	500	19	100	91	Ar′ = 3,5-CF_3Ph, 50 °C
1.6	**A**[b]	500	19	100	95	$RuCl_2$(**A**)(PPh_3)
1.7	**A**[b]	500	19	100	85	$RuCl_2$(**A**)(PPh_3), 75 °C
1.8	**A**[b]	50,000	92	99	94.3	3.75 mol/0.45 L of toluene/150 mL of NaOH

[a] Reaction conditions: in situ catalyst with ligand **A** and $RuCl_2(PPh_3)_3$; 2.3 mmol substrate (Fluorochem); 10−12 mL of toluene; 1 mL of 1 M aqueous NaOH; 25 °C; 20 bar. [b] Isolated $RuCl_2$(**A**)(PPh_3) complex.

of the efficient catalytic systems are patent protected, a new catalyst had to be found, and a technically feasible process had to be developed in order to produce >200 kg amounts of BTMP.

The key issues investigated during the course of the project were (i) to identify the best catalyst/ligand for a highly reproducible hydrogenation reaction that meets the defined specs (conversion >99%; enantioselectivity >94% ee; substrate/catalyst ratio (s/c) ≥10,000, preferably ≥20,000) and (ii) to carry out a quality risk analysis with emphasis on the hydrogenation reaction as basis for the up-scaling in the production reactor.

The timeline set for this project (from screening to pilot plant) was very ambitious. Solvias and its scale-up partner Novasep Synthesis Switzerland had a mere 2 months available to develop a pilot process and to manufacture the required amounts of BTMP. Here we describe the various tasks carried out in order to work out a pilot process and to manufacture the required amounts of BTMP on time and with the requested quality.

Ligand Screening and Optimization of the Reaction Conditions. The screening experiments were carried in 50-mL autoclaves under the standard reaction conditions established during the research phase using BTMA from Fluorochem.

Ligand Structure. On the basis of the results with various model substrates a number of different ligands were screened, and selected results are shown in Table 1. As the variations in enantioselectivity (ee 91−94%) were rather small (entries 1.1−1. 5), ligand **A** (R = *i*-Pr, Ar = Ph) was chosen for scale-up and further optimization and development since it is produced by Solvias on a kilogram scale and is also the cheapest of the tested ligands. As expected, the catalyst prepared in situ from ligand **A** and $RuCl_2(PPh_3)_3$ gave the same performance as the isolated one-component $RuCl_2$(**A**)-(PPh_3) complex (compare entries 1.1 and 1.6) which, however, sometimes showed an induction period of up to several hours. Despite this disadvantage, the isolated $RuCl_2$-(**A**)(PPh_3) complex was prepared in larger amounts and used in all further experiments because a one-component catalyst is easier to handle in a technical setting.

Optimization of Reaction Conditions. *Nature and Quantity of the Base.* Aqueous NaOH was clearly superior, weaker bases were not suitable (results not shown).

Effect of Pressure and Temperature (see Figure 2). It was shown earlier that relatively high pressure is needed for good

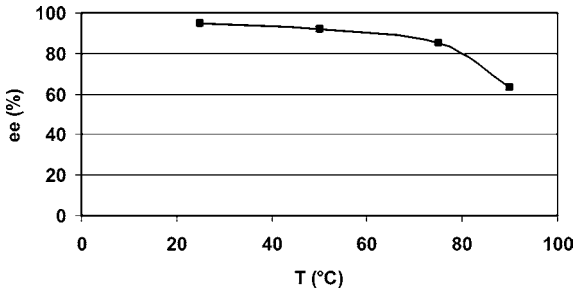

Figure 2. **Effect of temperature on ee (for reaction conditions see Table 1).**

reaction rates; 20 bar proved to be a good compromise between rate and equipment cost. While raising the temperature from 25 to 50 °C leads only to a slight decrease in ee, at 75 °C the ee drops to 85% (see entry 1.7). Finally, 25 °C and 20 bar were chosen to guarantee more process stability. Several experiments were carried out to determine the catalyst loading needed for a reaction time of <15 h. It must be stressed that TON and TOF strongly depend (among other things of course) on the purity of the substrate (see below). As scale-up experiments with the standard laboratory material from Fluorochem demonstrated, s/c ratios between 10,000 and 20,000 were possible, whereas at 50,000 full conversion was only reached after 92 h (see Table 2). Furthermore, it was also evident that substrate concentrations between 0.4 and >3 mol/L can be employed.

Quality Risks. Since many factors can affect the performance of a catalytic process, a thorough risk analysis was carried out to ensure a reliable manufacturing process. Here we will illustrate in some detail the effect of the BTMA quality, the most important factor affecting catalyst performance. BTMA of three different suppliers was tested, showing strongly different behavior as summarized in Table 3. Without any further purification, materials from suppliers 1 and 3 lead to reaction times of <20 h for complete conversion (entries 3.1 and 3.8), whereas BTMA from supplier 2 did not react under the standard conditions (entry 3.3)! Somewhat unexpectedly, distillation did not remediate the problem. Since the reaction is carried out under basic conditions, we measured the pH of the material both before and after distillation, and it turned out to be around 3. Extraction with aqueous KOH/brine and even more with KOH improved the conversion (entries 3.4 and 3.5), but only distillation over KOH led to very good catalyst performance (entries 3.6−3.7). All scale-up hydrogenations were per-

Table 2. **Scale-up results and effect of BTMA concentration[a]**

entry	BTMA mol	BTMA mol/L	s/c	time (h)	conv. (%)	ee (%)	comments
2.1	0.586	0.37	10,000	2.3	100	96.0	1.44 L of toluene, 60 mL $NaOH_{aq}$
2.2	0.586	0.37	20,000	21	100	95.9	1.44 L of toluene, 60 mL $NaOH_{aq}$
2.3	2.50	2.91	20,000	18	100	94.6	0. 3 L of toluene, 100 mL $NaOH_{aq}$
2.4	3.75	3.33	50,000	92	99	94.3	0. 35 L of toluene, 150 mL $NaOH_{aq}$

[a] Reaction conditions: 2.5-L autoclave, $RuCl_2$**A** $(PPh_3)_3$; substrate from Fluorochem; toluene; 1 M aqueous NaOH; 25 °C, 20 bar.

Table 3. **Effect of BTMA quality on catalytic performance[a]**

entry	BTMA	s/c	time (h)	conv (%)	ee (%)
3.1	Supplier 1, as supplied	10,000	19	100	95
3.2	Supplier 2, as supplied	10,000	19	no reaction	
3.3	Supplier 2, distilled	10,000	19	no reaction	
3.4	Supplier 2, extracted with KOH/brine	10,000	16	63	62
3.5	Supplier 2, extracted with KOH_{aq}	10,000	16	80	93
3.6	Supplier 2, distilled over KOH	10,000[b]	2.5	100	95
3.7	Supplier 2, distilled over KOH	20,000	20	100	95
3.8	Supplier 3, as supplied	10,000	19	100	95

[a] Reaction conditions: $RuCl_2$(**A**)(PPh_3) complex, 2.3−5 mmol substrate; 10−24 mL of toluene; 1−2 mL of 1 M aqueous NaOH; 25 °C 20 bar. [b] In 300-mL autoclave

Table 4. **Quality risk factors**

factor	assessment	measures/recommendations
inert gas (switch from Ar to N_2)	no problem with nitrogen better than 25 (>99.5%)	nitrogen 45 (>99.995%; O_2: <10 ppm)
autoclave purity	can be problematic	two-step washing and cleaning procedure (see Experimental Section)
autoclave inertization	important (safety and quality)	purge autoclave at least 5 times with 15 bar N_2
degassing of liquids and solutions	important (safety and quality)	apply at least six vacuum (1−2 mbar) /N_2 purge cycles
loading procedure	important	load catalyst and substrate separately, add $NaOH_{aq}$ immediately prior to start
reagent quality	important, not critical	technical quality toluene and hydrogen 25 can be used
BTMA concentration	not critical	10−75% (w/v) can be used
autoclave material	not critical	glass, SS316, Hastelloy B or C4 and Inconel are suitable

formed with the BTMA from supplier 3 which could be used without any further purification (pH 6.8).

The quality risk for several other process parameters was investigated, and a short summary is presented in Table 4.

Health and Safety. For the handling of toluene (Class 2 solvent), aqueous sodium hydroxide solutions, BTMA, and BTMP, standard safety procedures (suitable gloves, eye/face protection) and the usual safety-requirements regarding the handling of easily flammable liquids are mandatory. Hydrogen is toxic and forms explosive mixtures with air (explosion limit in air: 4.75 vol %). The apparatuses have to be tested at elevated pressure for leaks prior to the reaction (H_2 tightness), and a detection system for H_2 leaks during the run is recommended. The autoclave atmosphere has to be released through a special releasing device.

On the basis of DSC measurements and a reaction carried out in a reaction calorimeter, no significant chemical safety issues were identified.

DSC Measurement. BTMA, BTMP, the biphasic reaction mixture (in toluene/$NaOH_{aq}$), and a BTMP distillation residue in methanol or heptane showed small but uncritical decomposition exotherms between 0.7 and 2.3 mW usually observed between ~210 and 270 °C.

Reaction in a Mettler RC1 Reaction Calorimeter (1-L Hastelloy C4 autoclave). A heat flow of 102.4 kJ/mol BTMA or 399.7 kJ/kg BTMA, respectively, was calculated. MTSR (maximum temperature of the synthetic reaction under adiabatic conditions) was 49.5 °C, and TMRad (time to maximum rate under adiabatic conditions) was approximately 24 h. Because the hydrogenation of ketones is not very exothermic (approximately 25 kcal/mol) and no unusual decomposition tendency of BTMA and BTMP was observed, the hydrogenation was considered to be of low criticality.

Catalyst Removal. Catalyst removal is an issue in any homogeneous catalytic reaction since purity requirements in pharmaceutical production are very stringent. While crystallization, distillation, or extraction are the preferred techniques for removing impurities of any kind, these approaches are not always suitable or require more development time. In this situation, selective adsorption is a very attractive option.[7] For this reason we tested several commercially available adsorbing agents in a laboratory experiment using 30 g (117 mmol) of BTMA, 10.7 mg (0.012 mmol) of $RuCl_2$(**A**)(PPh_3)

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Table 5. **Adsorbent tests**[a]

entry	adsorbent (mg/50 mL solution)	residual Ru (ppm)	aspect
5.1	none	17.0	colorless[b]
5.2	Smopex 101 (100)	1.5	slightly pink
5.3	Smopex 105 (100)	4.8	slightly pink
5.4	Smopex 110 (100)	5.5	slightly pink
5.5	Smopex 113 (100)	5.1	slightly pink
5.6	Alox N (350)	3.0	slightly pink
5.7	active carbon Norit CA 1 (350)	0.3	colorless

[a] Conditions: The reaction solution was extracted twice with 12 mL of water and divided in 50-mL portions. The required amount of adsorbent was added and the mixture stirred at 23 °C for 45 min. After filtration over Clarcel, the filtrate was evaporated and the residue analyzed for Ru. [b] Crude BTMP was recrystallized from heptane.

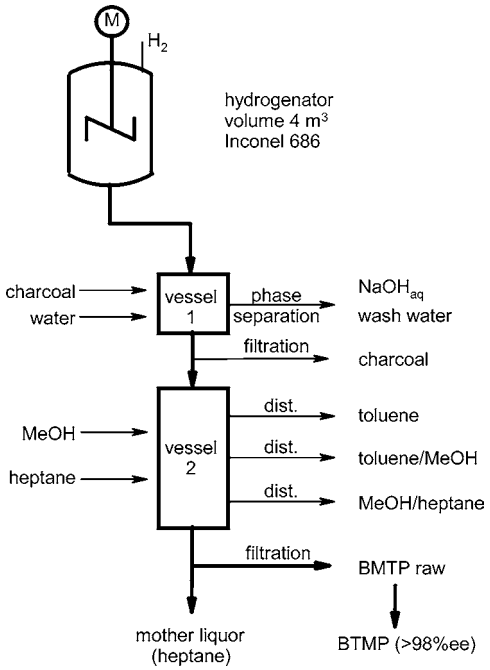

Figure 3. **Flowchart of the hydrogenation process.**

complex in 300 mL of toluene and 12.5 mL of 1 N NaOH (27 °C, 22 bar; 19 h). The results are shown in Table 5 and clearly show that Norit CA 1 (entry 5.7) is the adsorbent of choice not only removing most of the ruthenium but also leading to a colorless product.

Final Process. To produce the required amounts of BTME, the optimized process was run twice with 140 kg of substrate in a 4 m^3 hydrogenation reactor with an s/c ratio of 20,000 at 20 bar and 25 °C. Full conversion was reached after 15 and 11.5 h, respectively, despite the occurrence of an induction period when using the monocomponent $RuCl_2$-(**A**)(PPh_3) complex. Standard multipurpose equipment was used for work up as schematically shown in the flow chart depicted in Figure 3. After the reaction, ee's were 95.8 and 95.4% which improved to 98.6 and 97.7% after the crystallization of the BMTP, with an isolated yield of 70.1 and 70.7%, respectively. Overall, the process scaled very predictably, and no unforeseen issues appeared, allowing a timely delivery of product within the preset time frame of only 2 months.

Conclusions

In conclusion, we have shown that Ru/phosphine−oxazoline complexes are very robust, technically feasible catalysts for the enantioselective hydrogenation of aryl ketones. Very high turnover numbers can be achieved under relatively mild reaction conditions and with reasonable reaction times. The most critical parameter for good catalyst performance was the quality of the starting ketone. Scale-up to the >100 kg scale was unproblematic.

Experimental Section

Cleaning of the Autoclave. To ensure good catalyst performance the following two-stage cleaning procedure was applied. Subsequent to the typical cleaning procedure, the autoclave was first filled with up to 90 vol % of a mixture of toluene/aqueous sodium hydroxide (1 N) 24:1 v/v, and stirred at rt for 2 h. After the removal of this biphasic solution, the autoclave was washed with toluene and dried. Subsequently, an "etching" or conditioning hydrogenation with the intended catalyst $RuCl_2$**A**(PPh_3) was performed at about 10 times lower substrate concentration than typical. Instead of an expensive substrate, a model substrate such as acetophenone can be used.

Hydrogenation Procedure. Water (50.0 kg), 30% aqueous sodium hydroxide (7.2 kg, 54.0 mol), toluene (932 kg), and 3,5-bistrifluoromethyl acetophenone (140.2 kg, 547.3 mol) were combined in a 4000-L stainless steel vessel and five times inertized. $RuCl_2$**A**(PPh_3) (26 g, 0.03 mol, 5×10^{-5} equiv) was transferred by means of Schlenk technique as a suspension in toluene (0.87 kg) into an inertized 600-L stainless steel vessel. The catalyst was dissolved by the addition of degassed toluene (100 kg), and the diluted solutions were transferred to a 4000-L Inconel 686 autoclave. The liquid phase was saturated with hydrogen by pressurizing three times with 20 bar H_2. The hydrogenation was performed at 20 bar H_2 and 23 °C at an agitation speed of 250 rpm. After 15 h, in-process analysis indicated that the reaction was complete (<1% starting material by GC).

The hydrogen pressure was released and the autoclave subsequently purged with nitrogen. The biphasic reaction mixture was transferred to a 4000-L Inconel 686 receiver where the phases were separated. The organic layer was washed with water (50 kg) twice. Activated carbon Norit CA 1 (10 kg) was added, and the slurry was stirred for 45 min at ambient temperature. The suspension was filtered over a lens filter charged with filter aid Clarcel/Primisil (10 kg). Both receiver and lens filter were rinsed with toluene (50 kg). The filtrate was concentrated at 55 °C under reduced pressure (p = 150 mar) until 1200 L of distillate was collected. Then, methanol was added (1240 kg), and the remaining toluene was removed by azeotropic distillation (T = 65 °C; p = 1013 hPa). After 1500 L of distillate was collected, a second portion of methanol (240 kg) was added and distilled off (T = 65 °C; p = 1013 hPa). In-process analysis indicated that the residual methanolic solution contained less than 1% toluene (w/w; GC).

Heptane (575 kg) was added to the solution, and methanol was removed by azeotropic distillation (T = 60 °C; p = 100 hPa) until 850 L of distillate was collected. Then, a second

portion of heptane was added (315 kg) and again distilled off (T = 60 °C; p = 100 hPa). In-process analysis indicated that the residual solution contained less than 1% methanol (w/w; GC).

The solution was chilled to 32 °C by refluxing at reduced pressure (p = 100 hPa) and was inoculated with crystals of enantiomerically pure BTMP (ee > 99%). The temperature was reduced to 27 °C, and the mixture was stirred for 45 min. Then, the reactor content was chilled to 10 °C, and the crude BTMP was filtered off. The reactor and the filter cake were rinsed with cold heptane (T = 10 °C; 50 kg). Without discharging, the filter cake was melted with hot heptane (T = 85 °C; 372 kg). The hot solution was circulated until all material was dissolved. The solution was chilled to 32 °C by refluxing at reduced pressure (p = 100 hPa) and was inoculated with enantiomerically pure BTMP (ee > 99%). The temperature was reduced to 27 °C, and the mixture was stirred for 45 min. Then, the reactor content was chilled to 10 °C, and the precipitate was filtered off. The reactor and the filter cake were rinsed with cold heptane (T = 10 °C; 50 kg).

The product was discharged from the lens filter and dried in a tray dryer (T = 40 °C; p = 100 hPa) to afford pure BTMP (100.0 kg; 70.7% yield). Purity 100.0% (GC; sum of both enantiomers); ee 97.7% (GC); heptane 1.8% (w/w; GC); ruthenium <0.1 ppm.

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